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ORIGINAL ARTICLE

Association between cardiac function and metabolic factors including adiponectin in patients with acute myocardial infarction

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Summary
Background: Although several clinical studies have evaluated plasma adiponectin levels in response to chronic heart failure, little is known about the relation between cardiac function and metabolic factors including adiponectin in patients with acute myocardial infarction (AMI).
Methods and results: We analyzed 50 consecutive patients with AMI who had undergone successful coronary stent implantation. Echocardiography and blood sampling were performed at 1 week and 6 months after AMI. Blood was analyzed with regard to brain natriuretic peptide (BNP) and metabolic factors including plasma levels of adiponectin, lipid profile, and hemoglobin A1c (HbA1c). Plasma adiponectin levels were significantly increased at 6 months ($7.3 \pm 4.9\,\mu g/ml$) compared to those at 1 week (6.1 ± 3.7). BNP (from 156 ± 151 to $96 \pm 124\,pg/ml$) significantly decreased. In addition, BNP at 6 months was positively correlated with plasma adiponectin levels at 1 week ($y = 0.019\,x - 23.1$, $r = 0.537$, $P = 0.002$), while BNP at 6 months was not associated with maximal creatinine kinase after AMI. A multiple regression analysis was performed to analyze the relationship between BNP at 6 months and metabolic factors (plasma levels of adiponectin, lipid profile, HbA1c, blood pressure, age, sex, and body mass index) at 1 week after AMI. BNP at 6 months was most closely correlated with plasma levels of adiponectin at 1 week ($P = 0.045$).
Conclusions: Among the metabolic factors examined, a higher adiponectin level at 1 week is the predictor of a higher BNP as one marker of cardiac dysfunction at 6 months after AMI.

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Introduction

Metabolic syndrome (MetS), which consists of a clustering of cardiovascular risk factors, such as abdominal obesity, diabetes mellitus (DM), dyslipidemia, and hypertension, is associated with increased coronary artery disease (CAD) morbidity and mortality [1].

Adiponectin, which is a collagen-like plasma protein produced by adipose tissue, is known to play an important role in the development of MetS. A lower level of adiponectin is considered to be an independent risk factor for CAD, and is associated with patients with acute coronary syndrome (ACS) [2] and coronary complex lesions in stable CAD [3]. Adiponectin levels are lower in obese patients, and obesity is also known to be a risk factor for the development of chronic heart failure (CHF) [4]. Lower adiponectin levels appear to be a risk factor for CHF. Unexpectedly, recent studies have indicated that a higher body mass index (BMI) is associated with improved survival in patients with CHF [5,6]. In addition, plasma adiponectin levels are associated with an increased risk of mortality in patients with CHF [7] and increase according to the severity of CHF [8]. Thus, adiponectin may be a critical risk factor for mortality and the severity of CHF.

Much of the mortality following acute myocardial infarction (AMI) results from cardiac dysfunction after acute ischemia. Cardiomyocyte apoptosis has been thought to play a key role in this process. Shibata et al. reported that adiponectin protects against the development of systolic dysfunction after AMI through its ability to suppress cardiac hypertrophy and interstitial fibrosis, and also protects against myocyte and capillary loss in adiponectin-deficient mice [9]. Although many clinical studies have evaluated plasma adiponectin levels in response to CHF [5—8], little is known about the relation between adiponectin and cardiac dysfunction after AMI in humans. In this study, we assessed the associations between cardiac function and metabolic factors including plasma adiponectin levels in patients with AMI.

Methods

Subjects and design

The subjects included 50 consecutive AMI patients (men, 76%; age, 65 ± 11 years) who had initial coronary angiograms and significant coronary stenosis (>50% luminal narrowing) as defined by coronary angiography and who were successfully implanted with a stent. All of the enrolled patients received aspirin and ticlopidine. Follow-up coronary angiography was performed at 6 months. There was no cardiac event in any of the patients throughout the study. The ethics committee of Fukuoka University Hospital approved this study and written informed consent was obtained from each patient.

Patients did not have vascular disease (aortitis treated by prednisolone) or hepatic dysfunction (viral and nonviral, transaminases more than three times the normal value). Patients with low-density lipoprotein cholesterol (LDL-C) $\geq$140 mg/dl or triglyceride (TG) $\geq$150 mg/dl were diagnosed as dyslipidemic. Patients with systolic or diastolic blood pressure (SBP or DBP) $\geq$140 mmHg or 90 mmHg or who were under antihypertensive treatment were considered to have hypertension. Patients who were being treated for diabetes mellitus (DM) or who had symptoms of DM and a fasting blood glucose concentration $\geq$126 mg/dl were considered to have DM. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose DM.

Blood sampling

Blood sampling was performed at 1 week and 6 months after AMI. Plasma levels of adiponectin, brain natriuretic peptide (BNP), lipid profile, c-reactive protein (CRP), fasting glucose, and hemoglobin A1c (HbA1c) were measured. When CRP was less than 3 mg/l, a high-sensitivity assay for CRP (hs-CRP) was also performed. The concentrations of adiponectin in plasma were determined in duplicate by specific enzyme immunoassays (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. At our laboratory, the intra- and inter-assay coefficients of variation were each 5%.

Transthoracic ultrasound echocardiography

Echocardiography was performed before coronary angiography upon hospitalization. An experienced sonographer obtained all echocardiographic data, which were interpreted by an experienced staff echocardiographer. Comprehensive examinations were performed on all of the study patients, including M-mode, two-dimensional, conventional Doppler, and color Doppler echocardiography, at the time of coronary angiography. Left ventricular mass (LVM) was calculated as $1.04 \times \{[\text{LV internal dimension at end-diastole (LVDd)} + \text{intraventricular septal thickness (IVST)} + \text{LV posterior wall thickness (LVPWT)}]^3 - (\text{LVDd})^3\} - 13.6$ according to Devereux

et al. [10], and the LVM index (LVMI) was adjusted for body surface area.

Statistical analysis

Statistical analysis was performed using the Stat View statistical software package (Stat View 5; SAS Institute Inc., Cary, NC, USA). Categorical and continuous variables were compared by a chi-square analysis and one-way analysis of variance followed by post hoc Fisher's PLSD test. The Spearman correlation was used to examine the relation between continuous variables. Multiple regression analysis was used to assess the correlation of echocardiographic parameters or metabolic factors to BNP at 6 months. Data are presented as the mean and standard deviation (SD). Significance was considered to be less than 0.05 unless indicated otherwise.

Results

Patient characteristics

The baseline characteristics of the subjects are shown in Table 1. The subjects consisted of 38 men and 12 women with a mean age of 65 ± 11 years. Twenty-seven subjects had hypertension and dyslipidemia was present in 35 subjects. On stent implantation procedure, 8 types of stent were used and the average of length, diameter, and maximal inflation pressure were 20 ± 5 mm, 3.3 ± 0.3 mm, and 14 ± 3 atm, respectively.

Changes in BP, plasma levels of biochemical parameters

DBP was significantly reduced at 6 months compared to those at 1 week, while there was no change in SBP (Table 2). LDL-C was significantly decreased at 6 months and HDL-C was significantly increased at 6 months compared to those at 1 week, while there was no change in HbA1c, fasting glucose, and TG. Plasma adiponectin levels were significantly increased at 6 months compared to those at 1 week, and there were no differences in plasma adiponectin levels at 1 week and 6 months between the presence and absence of DM, hypertension, dyslipidemia, and treatment with statins or angiotensin receptor blockers (ARBs) (data not shown). In addition, the plasma adiponectin levels in women tended to be higher than that in men at 1 week ($P = 0.056$), while there was no difference at 6 months ($P = 0.662$) and no changes in the values from 1 week to 6 months ($P = 0.861$). The levels

Table 1 Patient characteristics.

Age (years)	65 ± 11
Male (%)	76
BMI (kg/m^2)	23.5 ± 3.5
Hypertension (%)	54
SBP (mmHg)	126 ± 25
DBP (mmHg)	76 ± 14
DM (%)	34
HbA1c (%)	5.9 ± 1.1
Fasting glucose (%)	99 ± 19
Dyslipidemia (%)	70
LDL-C (mg/dl)	126 ± 27
TG (mg/dl)	130 ± 73
HDL-C (mg/dl)	41 ± 11
Smoking (%)	68
Uric acid (mg/dl)	5.5 ± 2.1
Medication (%)	
ARB	50
ACEI	0
CCB	14
β-blocker	18
Diuretics	28
ISDN	20
Nicorandil	64
Statin	100
Number of vessels	
1 (*n*)	26
2 (*n*)	14
3 (*n*)	10
Target vessel	
RCA (*n*)	26
LCx (*n*)	2
LAD (*n*)	22
Stent implantation procedure	
Types	
Be stent (*n*)	1
Bx Velocity (*n*)	12
Duraflex (*n*)	3
Eepress 2 (*n*)	2
Multi-link (*n*)	20
Radius (*n*)	10
S660 (*n*)	1
Tsunami (*n*)	1
Length (mm)	20 ± 5
Diameter (mm)	3.3 ± 0.3
MIP (atm)	14 ± 3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ISDN, isosorbide dinitrate; RCA, right coronary artery; LCx, left circumflex artery; LAD, left anterior descending artery; MIP, maximal inflation pressure.

Table 2 BP, plasma levels of biochemical parameters at 1 week and 6 months.

	1 week	6 month	*P*-value
SBP (mmHg)	126 ± 25	123 ± 17	NS
DBP (mmHg)	76 ± 4	72 ± 9	0.049
HbA1c (%)	5.9 ± 1.1	5.8 ± 0.8	NS
Fasting glucose (%)	99 ± 19	100 ± 24	NS
LDL-C (mg/dl)	126 ± 27	98 ± 21	<0.001
TG (mg/dl)	193 ± 32	142 ± 89	NS
HDL-C (mg/dl)	41 ± 11	47 ± 11	<0.001
Adiponectin (μg/ml)	6.1 ± 3.7	7.3 ± 4.9	0.009
BNP (pg/ml)	156 ± 151	96 ± 124	0.013
CRP (mg/l)	32 ± 46	2 ± 3	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide. hs-CRP, high-sensitive C-reactive protein; NS, not significant. When CRP was less than 3 mg/l, a high-sensitivity assay for CRP (hs-CRP) was also performed.

of BNP and CRP were significantly decreased at 6 months.

Changes in echocardiographic parameters

Among echocardiographic parameters, only IVST at 1 week was significantly lower than that at 6 months, whereas there were no changes in other parameters (Table 3).

Simple regression analysis between BNP and echocardiographic parameters at 6 months

Next, we analyzed the association between BNP and echocardiographic parameters at 6 months. Although there were no relationships between BNP at 6 months or IVST and PWT at 6 months, BNP at 6 months was significantly and positively correlated with LVMI ($r = 0.491$, $P = 0.003$). In addition, BNP at 6 months was significantly and positively correlated with LVDd ($r = 0.411$, $P = 0.030$) and LVDs ($r = 0.592$, $P < 0.001$) at 6 months, and BNP at 6 months was significantly and negatively correlated with ejection fraction at 6 months ($r = -0.629$, $P < 0.001$). Multiple regression analysis was performed to analyze the relationship between BNP and echocardiographic parameters (LVDd, LVDs, IVST, PWT, EF, LVM, and LVMI) at 6 months. BNP at 6 months was most closely correlated with LVMI at 6 months (standardized regression coefficient = 1.012, $P = 0.036$).

Table 3 Echocardiographic parameters at post-stent or 1 week and 6 months.

Parameters	1 week	6 month	*P*-value
LVDd	51 ± 7	53 ± 7	NS
LVDs	36 ± 8	37 ± 8	NS
IVST	9 ± 2	8 ± 2	0.012
PWT	9 ± 2	9 ± 2	NS
EF	55 ± 12	57 ± 12	NS
LVM	214 ± 71	205 ± 69	NS
LVMI	131 ± 38	127 ± 43	NS

LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness; EF, ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; NS, not significant.

Correlation between BNP at 6 months and plasma adiponectin levels at 1 week and 6 months

BNP at 6 months was positively correlated with plasma adiponectin levels at 1 week ($y = 0.019\,x - 23.1$, $r = 0.537$, $P = 0.002$) (Fig. 1) and at 6 months ($y = 0.009\,x + 27.9$, $r = 0.379$, $P = 0.03$), while BNP at 6 months was not associated with maximal creatinine kinase after AMI ($r = 0.014$, $P = 0.941$).

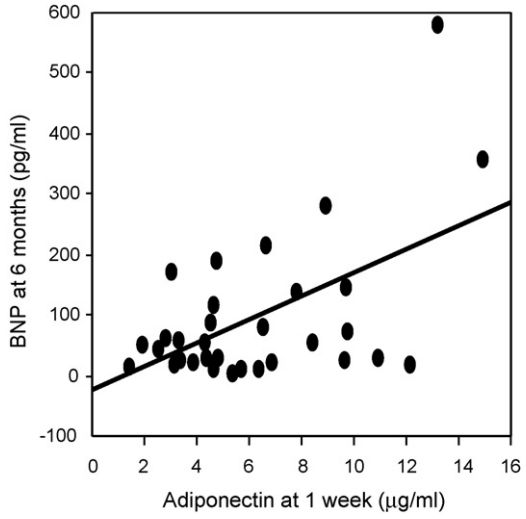

Figure 1 Correlations between BNP at 6 months after AMI and plasma adiponectin levels at 1 week ($y = 0.019\,x - 23.1$, $r = 0.537$, $P = 0.002$).

Table 4 Multiple regression analysis for predicting BNP at 6 months.

Factors	Standardized regression coefficient	*P*-value
Age	0.23	0.417
Sex	−0.13	0.600
BMI (kg/m^2)	−0.03	0.899
SBP (mmHg)	−0.07	0.826
DBP (mmHg)	0.26	0.446
HbA1c (%)	0.06	0.781
LDL-C (mg/dl)	−0.19	0.353
TG (mg/dl)	0.17	0.438
HDL-C (mg/dl)	−0.34	0.109
Adiponectin (μg/ml)	0.51	0.045

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

Association between BNP at 6 months and metabolic factors

Multiple regression analysis was performed to analyze the relationship between BNP at 6 months and metabolic factors (plasma levels of adiponectin, lipid profile, HbA1c, blood pressure, age, sex, and BMI) at 1 week (Table 4). BNP at 6 months was most closely correlated with plasma levels of adiponectin at 1 week ($P = 0.045$). Among the metabolic factors examined, a higher adiponectin level at 1 week after AMI was the strongest contributor to a higher BNP at 6 months after AMI.

Discussion

In this prospective study, we assessed the association between BNP and echocardiographic parameters or metabolic factors including adiponectin in patients with AMI. The present study indicated that BNP at 6 months after AMI as a marker of cardiac dysfunction was most closely associated with the plasma adiponectin concentration at 1 week after AMI. A higher plasma adiponectin level might be a predictor in the cardiac dysfunction after AMI.

Adiponectin has both anti-atherogenic and anti-inflammatory properties. Plasma adiponectin levels are negatively correlated with cardiovascular risk factors [12] and are lower in obese patients [13]. Since obesity is also associated with increased LV dilatation [14] and an increase in the incidence of HF [4], higher plasma adiponectin levels should be associated with a decreased risk of mortality in patients with CHF. In addition, Kojima et al. reported that low plasma adiponectin levels during post-AMI follow-up were associated with a poor prognosis in men [11]. In fact, the experimental studies indicated that adiponectin exerts beneficial effects on the heart after pressure overload or ischemia reperfusion injury in mouse models [15,16]. Moreover, adiponectin protects against the development of systolic dysfunction after MI in adiponectin-deficient mice [9]. These clinical and basic studies also suggest that adiponectin has cardiovascular protective effects. In contrast to this concept, higher plasma adiponectin levels predict mortality in patients with CHF. There is increasing evidence that adiponectin plays an important role in the development of CHF [5–7]. A recent study reported a significant association between plasma adiponectin levels and the severity of CHF [8]. Our study also indicated that higher plasma adiponectin levels might be a predictor of cardiac dysfunction after AMI. While our experiments were in progress, Inoue et al. reported serum high molecular weight adiponectin levels may serve as a predictor of future cardiovascular events in patients with CAD as well as a marker for severity of CAD [17]. With regard to the association between adiponectin and cardiac function, our results are consistent with those of Inoue et al., who reported that adiponectin level was negatively correlated with EF.

Since Shibata et al. [9] and Liao et al. [18] provided data to support the notion that adiponectin protected against the development of HF in adiponectin-deficient mice, adiponectin is believed to be essentially cardio-protective. In this study, there was no significant change in LVMI between 1 week and 6 months after MI. Progressive cardiac hypertrophy may be compensatory at the initial stage of MI. Apoptosis in cardiomyocytes may contribute to the progression of HF after MI [19], and cardiac dysfunction is associated with increased apoptosis in the infarct border zone after MI [20]. Since adiponectin overexpression attenuates cardiac hypertrophy [15,18] (since myocardial apoptosis and infarct size were markedly enhanced in adiponectin-deficient mice [21]), the patients with higher BMI in the present study might show a compensatory increase in plasma adiponectin levels to prevent hypertrophy. In support of this hypothesis, Nakamura et al. analyzed the changes in plasma adiponectin levels in CHF patients during early hospitalization [8]. Plasma adiponectin levels can rapidly respond to acute changes in hemodynamics, and these levels were reduced in association with improved cardiac function within only 3.3 days.

Plasma adiponectin levels were clearly and positively related to BNP levels in this study. This finding is consistent with a previous report [7]. Kistorp et

al. found a positive correlation between plasma adiponectin levels and N-terminal (NT) proBNP levels [7]. They hypothesized that natriuretic peptides indirectly stimulate adiponectin through increased lipid mobilization [22], although the mechanism is not clear. Next, they also found an association between NT-proBNP and BMI, while our data did not show a relationship between BNP and BMI. We cannot explain this discrepancy at this time. Further studies are needed to address these two issues.

The plasma adiponectin concentration is regulated by the presence of DM, hypertension, and dyslipidemia. In addition, medications against CHF [23] such as ARBs [24] have been shown to significantly increase the plasma adiponectin concentration. Although many factors affect adiponectin levels, there were no differences in plasma adiponectin levels at 1 week and 6 months between the presence and absence of DM, hypertension, dyslipidemia, or treatment with statins or ARBs in this study. Plasma adiponectin levels are lower in men than in women probably due to selective reduction by testosterone [25]. A recent study reported that plasma adiponectin levels are associated with future coronary events in men but not in women [26]. The pattern of changes in plasma adiponectin levels was also different between men and women after AMI [10]. In this study, while the plasma adiponectin concentration in women tended to be higher than that in men at 1 week, there was no difference at 6 months and no changes in the values from 1 week to 6 months. Moreover, we performed a multiple regression analysis to analyze the relationship between BNP at 6 months and metabolic factors including sex.

Although we only measured plasma adiponectin levels as cytokines, tumor necrosis factor (TNF)-α was reported to be increased in CAD and CHF [27]. Adiponectin may counteract TNF-α, and adiponectin inhibits the release of TNF-α from adipose tissue [28]. Plasma adiponectin levels correlated with plasma levels of TNF-α and BNP [8]. Other cytokines such as TNF-α may be more strongly associated with survival in patients with CHF.

Study limitations

This study considered a limited number of patients who underwent stent implantation after AMI. The results of this study represent only a selected group of patients and the sample size was relatively small, which limited our ability to determine the significance of associations. To confirm the results of this study, a larger population needs to be examined.

Conclusions

Our results clearly show an association between plasma adiponectin levels and BNP levels after AMI. A higher plasma adiponectin level at 1 week may be critical for predicting higher BNP levels as a marker of cardiac dysfunction at 6 months after AMI.

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